

Time window for recanalization in basilar artery occlusion

Speculative synthesis

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ABSTRACT

Basilar artery occlusion (BAO) is one of the most devastating forms of stroke and few patients have good outcomes without recanalization. Most centers apply recanalization therapies for BAO up to 12–24 hours after symptom onset, which is a substantially longer time window than the 4.5 hours used in anterior circulation stroke. In this speculative synthesis, we discuss recent advances in BAO treatment in order to understand why and under which circumstances longer symptom duration might not necrotize the brainstem and turn therapeutic attempts futile. We raise the possibility that distinct features of the posterior circulation, e.g., highly developed, persistent collateral arterial network, reverse filling of the distal basilar artery, and delicate plasma flow siding the clot, might sustain brittle patency of brainstem perforators in the face of stepwise growth of the thrombus. Meanwhile, the tissue clock characterizing the rapid necrosis of a typical anterior circulation penumbra will not start. During this perilous time period, recanalization at any point would salvage the brainstem from eventual necrosis caused by imminent reinforcement and further building up of the clot. *Neurology*® 2015;85:1806–1815

GLOSSARY

AICA = anterior inferior cerebellar artery; **BA** = basilar artery; **BAO** = basilar artery occlusion; **BASICS** = Basilar Artery International Cooperation Study; **CTA** = CT angiography; **DWI** = diffusion-weighted imaging; **IAT** = intra-arterial thrombolysis; **ICA** = internal carotid artery; **IVT** = IV thrombolysis; **MCA** = middle cerebral artery; **MRA** = magnetic resonance angiography; **mRS** = modified Rankin Scale; **OTT** = onset-to-treatment time; **pc-ASPECTS** = posterior circulation Alberta Stroke Program Early CT Score; **PICA** = posterior cerebral artery; **PCom** = posterior communicating artery; **PCS** = posterior circulation stroke; **PICA** = posterior inferior cerebellar artery; **PWI** = perfusion-weighted imaging; **RCT** = randomized controlled trial; **SCA** = superior cerebellar artery; **slCH** = symptomatic intracerebral hemorrhage; **TOF** = time-of-flight; **VA** = vertebral artery.

Basilar artery occlusion (BAO) is associated with high mortality (85%–95%) if recanalization does not occur. Evidence of the relative efficacies of different therapy protocols of IV thrombolysis (IVT) or intra-arterial thrombolysis (IAT) or mechanical endovascular treatment is based on retrospective or prospective patient cohorts, since there is only one randomized controlled trial (RCT) with 16 patients.¹ In a systematic analysis comparing the outcomes after variable protocols to achieve recanalization in BAO, there was only negligible likelihood of good outcome (2%) in the absence of recanalization, but reaching at least partial recanalization increased the odds of favorable outcome to 38%.² Based on largely empirical evidence, many stroke centers have adopted recanalization therapy protocols with time windows much wider than 4.5 hours from symptom onset, which is used for stroke thrombolysis in general. This article summarizes evidence and presents a hypothesis that assists in conceiving why we can help patients with BAO even after a long period after onset.

THE TIME WINDOW IN BAO RECANALIZATION PROTOCOLS The spontaneous recanalization rate of BAO within the natural course is not known, but is thought to be relatively low and not to exceed 20% within a clinically meaningful time window of 12–24 hours.³ Indeed, many centers apply thrombolysis for BAO up to 12–24 hours after symptom onset.^{2,4,5} In the systematic analysis of BAO case series, the treatment delay fluctuated between 7 and 48 hours after symptom onset.² In the IVT series, the fraction treated within

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12 hours was 77%, and within 6 hours 29%. In the IAT series, the corresponding fractions were 76% and 42%, respectively. In the Helsinki IVT cohort (n = 184),⁶ favorable outcome (modified Rankin Scale [mRS] 0–3) was achieved in 39% of those treated within 6 hours, in 36% within 6–12 hours, and in 36% above 12 hours. If patients with extensive infarction already at baseline are excluded, at least 50% reached mRS 0–3 even when treated beyond 12 hours. The rates of the 2 worst outcomes (mRS 5 or 6) were comparable in these 3 time windows: 51%, 57%, and 50%, respectively. Recanalization took place in 82%, 70%, and 75%, respectively.⁶ Timing of treatment has been a significant prognostic predictor in univariate analyses, but not in multivariable analyses adjusted for extent of baseline ischemic changes.^{6,7} Halving the onset-to-treatment time (OTT) after 2005 in Helsinki did not translate into therapeutic improvement (Lindsberg et al., unpublished data, 2015). These data do not back a firm time window for therapies attempting to reverse BAO.

In a recent analysis of the Basilar Artery International Cooperation Study (BASICS) registry (n = 619), Vergouwen et al.⁸ found that the prognosis was related to the time from symptom onset and patients with severe strokes at presentation treated beyond 9 hours after onset had poor clinical outcome. Unlike pivotal recanalization studies in anterior circulation stroke, patients with extensive infarct signs already at baseline were not excluded in the BASICS registry. In the Helsinki series of BAO (n = 184), a similar decay of therapeutic efficacy is seen beyond 9 hours, but this time dependency disappeared when the results were adjusted for the extent of baseline ischemia (posterior circulation Alberta Stroke Program Early CT Score [pc-ASPECTS]).^{6,9} Patients treated later than 9 hours were simply more likely to have extensive infarctions before treatment.

RCTs of stroke have usually excluded patients presenting with characteristic posterior circulation symptoms. Therefore the time window for recanalization in posterior circulation stroke has not been ascertained in RCTs. Many published case series have recruited patients with substantially longer symptom times than considered suitable for the anterior circulation; up to 4.5–6 hours for IVT or IAT and 8 hours for mechanical thrombectomies.⁴ This has created an array of speculations, where, e.g., different collateral circulation patterns or fewer hemorrhages due to lesser infarct volumes have been conceived to increase the ischemia tolerance of brain tissue in the BA territory.¹⁰

COLLATERAL BLOOD FLOW DYNAMICS DURING BAO Once the trunk of the basilar artery (BA) has been occluded by a sudden (thrombo)embolus, blood pressure at the junction of posterior cerebral arteries

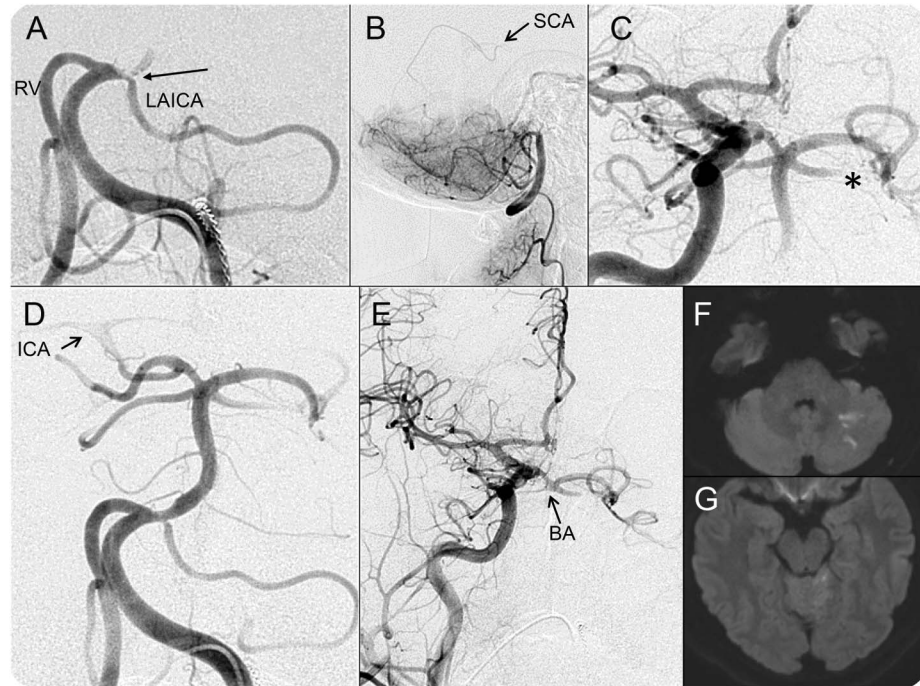
(PCAs) drops immediately. Depending on the individual vascular anatomy, blood flow within the circle of Willis is partially diverted from the anterior circulation through posterior communicating arteries (PComs) to fill this relative void and supply blood flow to the PCAs. Depending on the level at which the BA trunk is occluded, there will probably be reverse filling (reflux) to the distal BA, maintaining the patency of the superior cerebellar artery (SCA) branching from it as well as any number of perforator trunks and lateral, circumferential arteries that remain unblocked by the clot (see figures 1, 2, 4, and 9 from reference 11). This phenomenon is observed frequently when individuals with varying degrees of vertebral artery (VA) or even BA stenosis/occlusion are examined electively with digital subtraction angiography of the anterior circulation, and reversed filling of the distal BA can be observed to augment distal basilar patency also during the acute phase of BAO (figures 1C, 2C, and 3, A and B).

The significance of reverse flow gradient into BA also underlies the rationale of therapeutic stepwise VA occlusion in the treatment of true giant fusiform BA aneurysms. Before the advent of flow-diverting stents, this procedure was the only way to try to prevent rupture by lessening the pressure and flow inside the sac. Naturally, the sufficiency of the BA reverse flow had to be tested during acute temporary occlusion, which proves its existence also in the acute setting of complete vertebrobasilar occlusion.^{12,13} Detecting the reverse flow in the upper BA in the acute BAO setting would require selective catheterization of the cerebral arteries. This is not routinely done if the BAO has been diagnosed with CT angiography (CTA). CTA may demonstrate minute blood flow around the clot, but not its direction. Time-of-flight (TOF) magnetic resonance angiography (MRA) is ineffective in showing very slow or reverse flow in the BA because physical properties of TOF MRA require fast blood flow to produce visible flow enhancement.

Reverse flow from the PCom may augment residual circulation in the branches distal to the BA clot and, depending on the pressure gradient, may help maintain minute flow within the oligemic region. A small BAO series (n = 20) raised the idea that effective collateral flow to the BA may prolong ischemia tolerance and lead to more favorable outcomes.¹⁴ Of patients with collateral filling of the distal BA, 5 (83%) had a good neurologic outcome and 1 did not. Of those without collateral flow, 1 (17%) had a good neurologic outcome and 5 did not. Additional recent studies have corroborated the significance of collaterals as a prognostic predictor.^{7,15,16}

A second distinctive feature of collateral flow in BAO is the redundant blood supply from the VAs.

Figure 1 Images from a 47-year-old man with CT angiography–confirmed tandem occlusion of the proximal BA and left SCA



Digital subtraction angiography (DSA) of the left, dominant vertebral artery (VA) (A) confirms proximal basilar artery (BA) occlusion (arrow) about 5 mm distally from the junction of both VAs and at the origin of the dominating left anterior inferior cerebellar artery (LAICA). Reflux to the right vertebral artery (RV) is evident. Lateral projection of the early venous phase of left vertebral artery injection (B) shows a faint retrograde filling of the left superior cerebellar artery (SCA), but no opacification of the distal basilar artery. Right internal carotid artery (ICA) injection (C) demonstrates retrograde filling of the distal basilar artery and shows a thrombus also in the mesencephalic segment of the left SCA (asterisk in C). After stentriever thrombectomy of the basilar artery, left vertebral injection (D) shows antegrade flow in the BA with reflux into the right ICA. Control DSA of the right ICA after recanalization of the BA (E) shows faint opacification of the distal BA due a balanced flow backward and forward. Diffusion-weighted MRI (F, G) shows small, scattered ischemic lesions in the left SCA territory. The brainstem, however, was spared despite 7 hours of thromboembolic occlusion of the proximal BA.

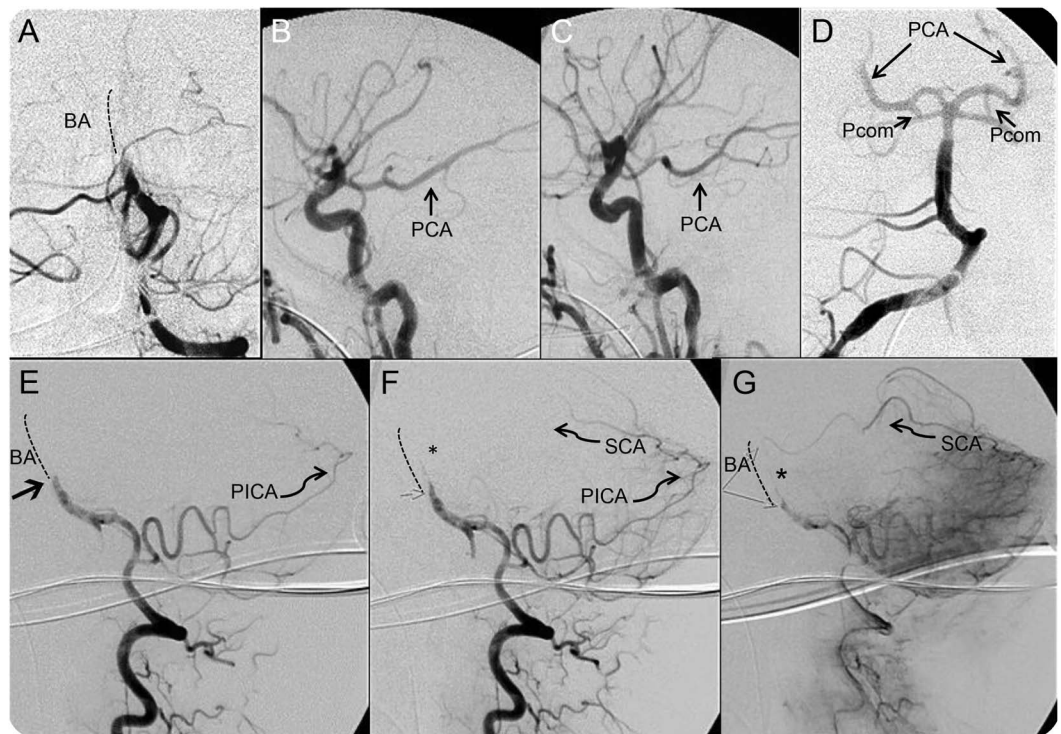
When the BA is blocked usually one VA remains open, i.e., the origin of at least one and often both posterior inferior cerebellar arteries (PICAs) are open. In addition, PICAs can be supplied by reverse flow in the anterior spinal artery, which originates unilaterally or bilaterally from the distal VA or PICA. In the cervical segment, the anterior spinal artery is well supplied by branches of the ascending and profound cervical arteries, which can compensate unilaterally or bilaterally occluded VAs.¹⁷ PICA is a strong collateral to the anterior inferior cerebellar artery (AICA) and SCA and thus to the brainstem perforating arterioles (figures 2, E–G, 3E, and 4, A–D). In BAO, this system may as well maintain brainstem vitality for significant periods if the clot does not gradually extend to block the perforating arteries.

THE RADICULAR AND ANASTOMOTIC BRAINSTEM VASCULAR SUPPLY One way to comprehend the delicate layout of the vasculature arising from the BA is to inspect the conceptual homology of the anatomical layout of vertebrobasilar and spinal arteries. The BA can be viewed to be formed by fusion of the longitudinal

neural system, which in its most primitive form consists of loosely connected channels running along the ventral surface of the brainstem. Later during fetal development, the channels will form longitudinal arterial circulations that will fuse on the ventral pontine surface to form the BA. Lasjaunias et al. viewed the arterial circulation of the brainstem and cerebellum as natural extensions of the segmental, radicular vascular layout found in the spinal cord (figure 5; see www.neuroangio.org). Lescher et al.¹⁸ have recently utilized high-resolution angiographic techniques to further visualize this concept.

If one considers the BA to be an extension of the anterior spinal artery, and its branches and perforators as homologs of the coronary and sulco-commissural arteries of the segmental spinal circulation, the relationship between the sequential buildup of an ascending clot and stepwise intensified clinical course reflecting successive brainstem infarctions makes perfect sense (figure 6A). This concept of stepwise growth of the BA thrombus is compatible with the clinical course characterized by repeated periods of sudden worsening of clinical symptoms before

Figure 2 Digital subtraction angiography images of a 42-year-old woman with right VA dissection and basilar thrombosis show the potential collateral routes that can maintain blood flow to the posterior circulation during BAO



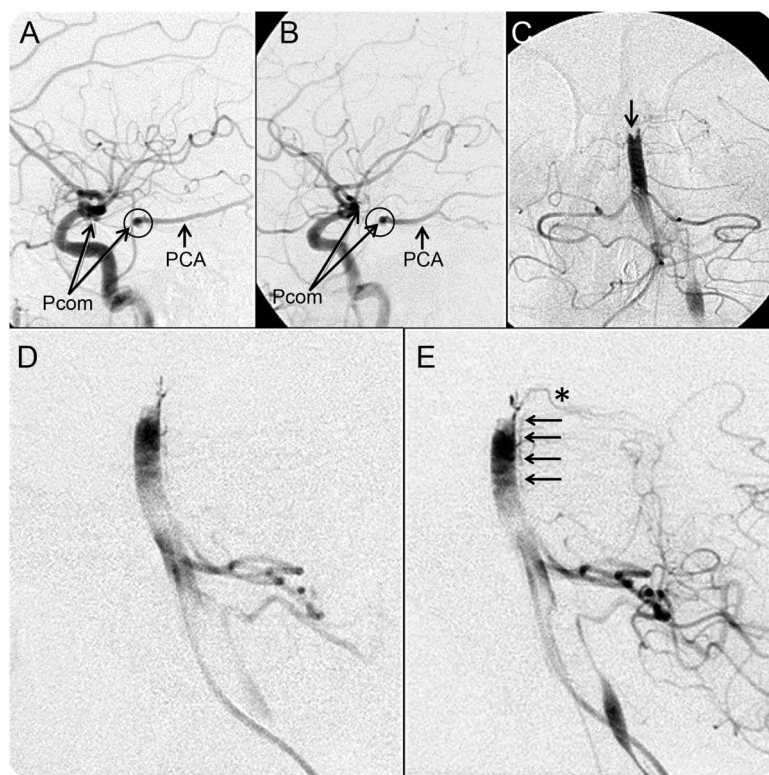
The clinical information and technical angiographic details of this case have been published previously.³² Left vertebral artery (VA) injection (A) demonstrates the thrombosed basilar artery (BA) segment (dotted line), beginning distal to anterior inferior cerebellar artery origins. Injections to right (B) and left (C) common carotid arteries during BA occlusion (BAO) show filling of both posterior cerebral arteries (PCAs) and basilar tip from the anterior circulation. Immediately after BAO recanalization, right VA injection (D) shows patent basilar artery, opacification of both PCAs, and opacification of both posterior communicating arteries (PComs) connected to the anterior circulation. There is diminished contrast attenuation in the PCAs and distal BA, confirming pressure transmission from the anterior circulation via the PComs into the basilar tip and distal BA. This type of pressure condition (functional arterial pressure immediately distal and proximal to the basilar thrombus) may prevent the thrombus from adhering tightly to the basilar artery wall and facilitate minute capillary flow around the thrombus. Slightly time-shifted systolic pressure gradients pounding the clot from opposite directions can generate piston-like movement or stepwise migration of the nonadherent clot. During BAO, left VA injection (E-G) shows that the distal BA also receives collateral flow through leptomeningeal anastomoses from left posterior inferior cerebellar artery (PICA) to distal branches of the left superior cerebellar artery (SCA). The flow direction in the right SCA is reversed (arrows). Slow, small-volume flow can also be seen between the thrombus and the BA wall in the late phases of the DSA run (F and G, asterisk). As the brainstem perforators directly originate from the periphery of the BA trunk, such minute flow might be able to sustain brainstem viability for a period of time during BAO.

full-blown BAO with locked-in syndrome, tetraplegia, and coma.

Detailed anatomical studies have demonstrated that a considerable amount of artery-to-artery anastomoses exist between the superficial brainstem arteries, but there is a lack of anastomoses between the internal brainstem arteries.¹⁹ In fact, these internal arteries can be considered as “the other cerebral end arteries.”¹⁹ So, a considerable network of anatomical anastomoses, and recruitment of potential anastomoses and above described collaterals arising from anterior and vertebral circulation, can assist in maintaining the larger supplying superficial arteries patent in acute BAO (figure 2, E–G and 3E). However, once the penetrating internal brainstem arteries lose patency, the irreversible necrosis will ensue rapidly.

CHARACTERISTICS OF BASILAR CLOT Empirical knowledge from long-lasting endovascular facilities supports a few distinctive features of BA clots. These clots are not so tightly compacted or tethered to the vascular wall compared with clots lodged elsewhere in the cerebral vessels. In fact, on repeated imaging, the clots seem to be roving a bit. This may relate to systolic-diastolic pressure amplitudes lower than, e.g., the anterior circulation, and to the fact that the distal pressure is not zero and is fluctuating through the cardiac cycle. 4D phase-contrast MRI pulsatile flow velocities have revealed that the systolic pressure peak is mounted a few milliseconds sooner to the internal carotid artery (ICA) bed than in the BA.²⁰ On lateral projections, often a thin layer of open lumen exists

Figure 3 Digital subtraction angiography images of a 68-year-old man with BAO



Right (A) and left (B) internal carotid artery injections show filling of the basilar tip (circle) and both posterior cerebral arteries (PCAs) from the anterior circulation, despite small-caliber posterior communicating arteries (PComs) (narrow vessel segments between the arrows). Selective contrast injection through a 5F aspiration catheter with its tip immediately proximal to the basilar artery occlusion (BAO) (C) outlines the thrombus with its convex border contrasted to the open vessel (arrow). Pontine perforators above the thrombus are faintly visible. Lateral projections of the superselective basilar artery (BA) injection (D, E) visualize the collateral network between the perforating arteries at the ventral brainstem surface: this can be recognized as a fine contrast line immediately dorsal to but still clearly separate from the BA lumen (arrows in E). The origin of perforators from this collateral network can be seen at the level of the BAO and short distance distal to it. In addition to recruitment of collateral flow from the anterior circulation and the pontine collateral network, there was leptomeningeal flow to the distal BA from the posterior inferior cerebellar artery similarly to case 1 (not shown). Reverse flow from the SCA is evident (asterisk in E). The patient presented with sudden loss of consciousness, but recovered to modified Rankin Scale score 1 after basilar thrombus aspiration, with only a small right thalamoperforator infarct at his follow-up MRI.

between clot and the dorsal origins of the brainstem perforators. Milliseconds apart, the systolic pressure waves are pounding the clot from the opposite directions. This may permit an element of plasma flow, facilitated by the minute piston-like migrations of the still nontethered blood clot. This oil around the piston may keep the perforators patent longer than if their origins were occluded by a tightly attached clot. Examples of the described plasma flow are seen in figures 2, F and G, and 4, D and E, and illustrated schematically in figure 6B. This is exclusively seen in the BA, but not at all in occlusions in the anterior circulation such as middle cerebral artery (MCA) occlusions.

This scenario would explain the common empirical observation that BAO is seemingly much more

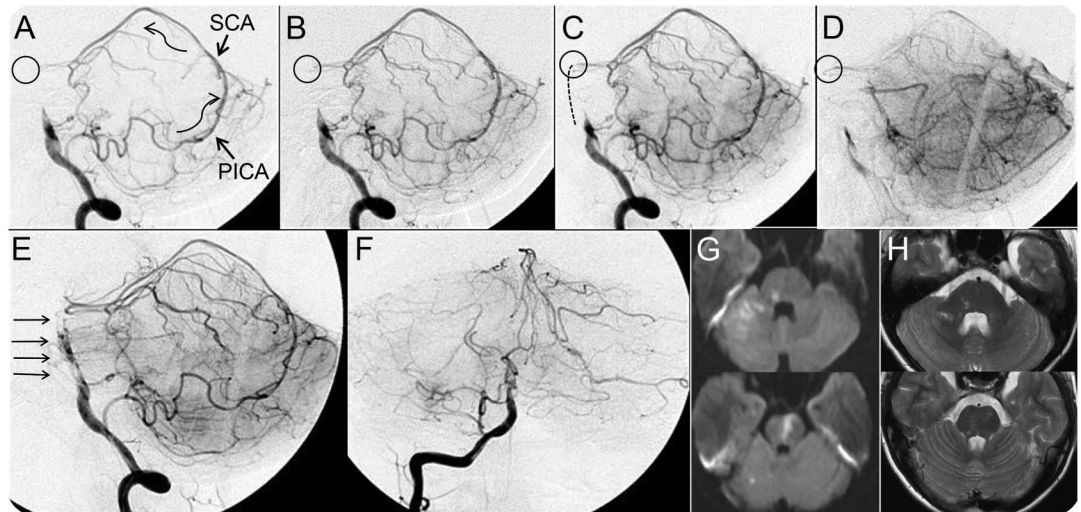
prone to reocclusion after thrombolysis compared with anterior circulation. The short-acting fibrinolytics may initially only detach the clot from the vascular wall, but without anticoagulation, thrombectomy, or longer lasting fibrinolytics, the clot will build up again, allowing the clinical syndrome to reappear.

The above considerations may also explain why thrombus aspiration is generally much easier in the BA than in the anterior circulation. The BA clots may also be less compacted, perhaps reflecting a higher water content. Due to the bidirectional arterial access, fibrinolytics may penetrate the clot more efficiently than in the MCA or ICA, which could explain why the recanalization rates of systemic thrombolysis are significantly higher in the BA. The degree of collateral circulation was recently shown to significantly promote recanalization.¹⁶ Furthermore, we have shown that contrary to the MCA clot, where 8 mm has been demonstrated to be a cutoff length for efficacy of IVT, there is no such cutoff for BAO thrombus.^{21,22}

IS THERE A PENUMBRA IN BAO? In their report of 10 individuals with acute BAO, Ostrem et al.¹⁰ obtained brain scans on average 4 hours 10 minutes after onset and found evidence of diffusion-weighted imaging (DWI)–perfusion-weighted imaging (PWI) mismatch in 5 patients, which included brainstem, cerebellum, and posterior cerebral hemispheres. This mismatch comprised 49%–99% of the total perfusion abnormality on early scans and did not entirely proceed to infarction following post-thrombolytic clinical improvement. Furthermore, in no case was there a reversal of diffusion abnormality in the brainstem or cerebellum. It could not be determined whether the pretreatment perfusion deficit represented oligemia rather than penumbra. We have not found additional reports of reversal of prethrombolytic DWI or PWI lesions within the posterior fossa, but there are technical difficulties in imaging penumbra-like flow conditions in the posterior fossa, as noted by others.^{23,24} However, the absence of BA territory circulation in the vast literature of ischemic penumbra is striking. In fact, considering perforant internal brainstem arteries as the other cerebral end arteries¹⁸ would actually suggest that, in line with the vulnerable region of hemispheric deep penetrating arteries, no penumbra can exist in the pons after the internal arteries have been occluded.

OTHER POTENTIAL EXPLANATIONS FOR LONG TIME WINDOW In BAO, the exact onset of symptoms has often been an issue. In a series of 85 patients with postmortem verified basilar or bilateral distal VA occlusions, onset was sudden in 20 patients; sudden, but preceded by prodromal symptoms in 11 patients;

Figure 4 Digital subtraction angiography (DSA) and MRI of a 9-year-old boy with BAO



The patient presented with ataxia, somnolence, seizures, and impaired consciousness. DSA demonstrated absent left posterior communicating artery (PCoM) and hypoplastic right PCoM. The lateral DSA projection of the right vertebral artery (VA) injection (A-D, frames shown at 1-second intervals) show that extensive collaterals provide flow to the basilar tip (circle) from posterior inferior cerebellar artery (PICA) via superior cerebellar artery (SCA). During the early and late venous phase at 6-7 seconds after injection (D, E), small perforating arteries can be recognized at the site of the basilar artery occlusion (BAO) (dotted line in C) and distal to it. After intra-arterial local thrombolysis with 750,000 IU urokinase 12 hours after symptom onset, lateral (E) and anteroposterior (F) views of the right VA injection show partial recanalization. Thrombus is still visible inside the BA lumen in its middle and distal segment (arrows, E). The brainstem perforators, however, are better visualized. On admission, diffusion-weighted MRI (G) already shows ischemic lesions in the right cerebellum, right posterolateral pons, and left paramedian anterior pons. Follow-up imaging (H) shows no additional ischemic lesions in the pons, even though the basilar artery flow could not be completely restored. In this case, minute flow around the margins of the thrombus may have been sufficient to maintain brainstem vitality. Several sources of the collateral flow can be visualized with DSA, but it is also possible that other collateral flow networks remain below its spatial resolution (approximately 200 μ m in this case).

and progressive in 54 patients.²⁵ Fifty-three patients had prodromes that cleared completely (TIA) before the start of a progressive or sudden onset. Half of these patients had their first symptoms during the 2 weeks before admission, but the rest had their TIA longer ago. In our understanding the onset of BAO should be limited to the monophasic course of acute BAO symptoms, which can be gradual, progressive, and full-blown at the outset.

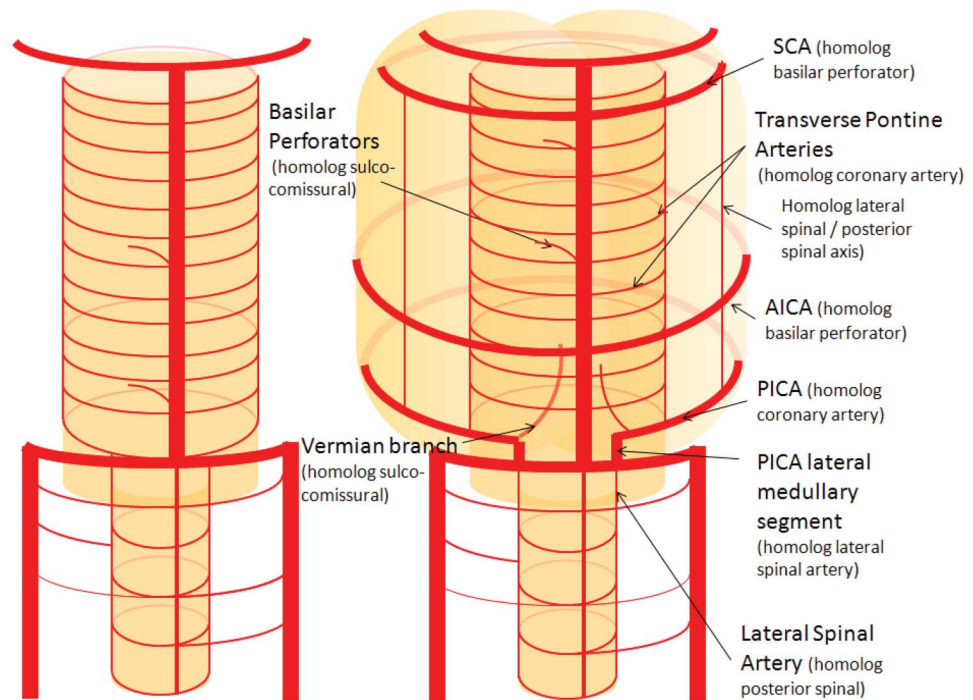
It has been suggested that the presumably longer time window for BAO recanalization therapies could be attributed to the relative scarcity of post-thrombotic symptomatic intracerebral hemorrhage (sICH), the most feared complication ruining the benefits of stroke thrombolysis.¹⁰ To this end, Sarikaya et al.²⁶ compared the post-thrombotic outcomes of 95 patients with posterior circulation stroke (PCS) with those of 788 patients with anterior circulation stroke and found that PCS was an independent predictor of lower sICH frequency ($p = 0.001$). In our large consecutive series of BAO thrombolysis, where good outcomes were strikingly not limited to short OTTs, increased OTT did not influence rates of sICH.⁶

Does the caudal brain have physiologically longer tolerance against tissue ischemia? Indeed, paramount

ultrastructural differences exist between phylogenetically diverse CNS structures. For example, the human cerebellum contains more neurons than the rest of the brain combined and the blood supply is characterized by a lack of anastomoses between the cortical penetrator branches.^{27,28} Not much is known of the patency of CBF autoregulatory capacity in the cerebellum and brainstem. Using transcranial Doppler and inhalation of CO₂, Reinhard et al.²⁸ demonstrated that cerebellar autoregulation was at least as efficient as that in the MCA territory. The vertebrobasilar circulation has less developed autonomic innervations, which has been linked to a lower autoregulatory ability in the PCA,²⁹ while the autoregulatory response and CO₂ reactivity of the BA have been found equal to the MCA.³⁰ However, these observations cannot be extended beyond hemodynamic and physiologic fluctuations to provide an answer.

HYPOTHESIS Why should the benefit of recanalization be less time-dependent in BAO than in anterior circulation occlusions? This counterintuitive point could arise from the anatomical vascular layout of the brainstem being different from that in usual anterior circulation strokes. To explain this, we

Figure 5 Lasjaunias' view of analogy of pontine circulation with spinal radicular segmental circulation



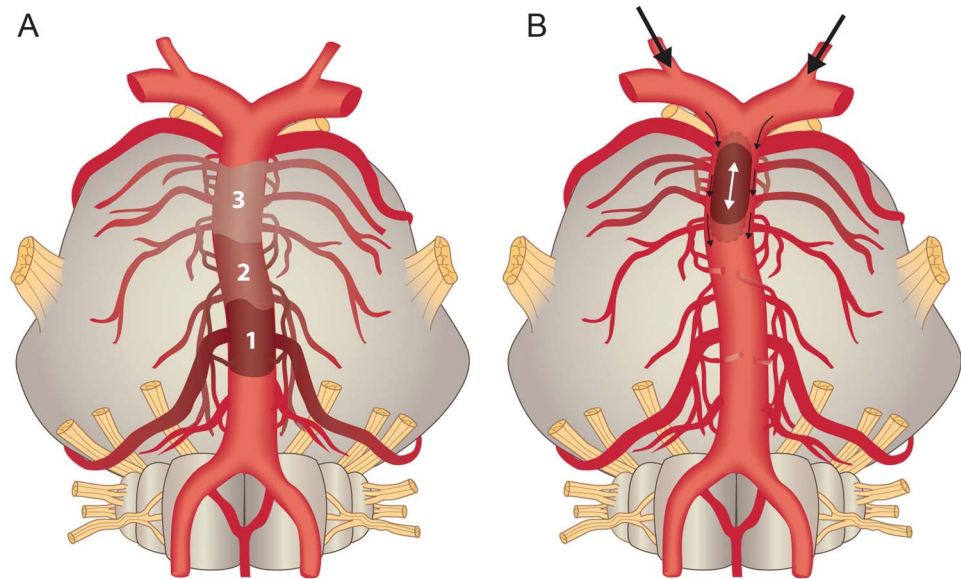
The image on the left shows the brainstem alone with schematic illustration of vertebrobasilar system with frequent transverse perforators (transverse pontine arteries). The image on the right, with cerebellum shown, portrays superior cerebellar artery (SCA), posterior inferior cerebellar artery (PICA), and anterior inferior cerebellar artery (AICA) as perforators, which are enlarged to take over the territory of cerebellar hemispheres. This perspective makes it straightforward to comprehend multiple SCA, PICA, and AICA variations found often within the vertebrobasilar arterial system. This segmental metameric organization applies to the posterior circulation at the levels of the medulla oblongata and pons. The upper part of the posterior circulation supplying the mesencephalon (distal to the site of fetal trigeminal artery, including the basilar tip) is embryologically part of the anterior circulation and lacks metameric organization. At birth, the relative importance of the anterior and posterior circulations in the mesencephalic blood supply depends on the time and individual pattern of fetal trigeminal artery involution. Figure courtesy Maksim Shapiro, MD (www.neuroangio.org). Reproduced with permission.

propose several vascular mechanisms that most often act simultaneously, but this depends on the individual clot location, location of local atherosclerotic plaques, and individual developmentally determined vascular anatomy.

1. A blood clot lodged in the BA will create a reverse circulation, arterial backflow from the circle of Willis through the PComs to the distal BA, which either directly from BA perforators or through recruiting and fueling the anastomotic and collateral vascular networks will maintain the vital brainstem structures viable for a considerable time if the clot does not enlarge and the brainstem does not have lethal ischemia. The prerequisite for this in terms of individual anatomy would, of course, be sufficient patency of PComs, and a relative importance of the fetal anterior circulation in the mesencephalic blood supply. In our understanding, in the anterior circulation there is no similar chance of emergency reserve of arterial blood to supply a relatively small volume but critical brain area that would be prognostically as decisive as the

brainstem. Who knows if this peculiar arrangement represents a phylogenetic construct to secure the vitality of brainstem in various vascular or hemodynamic catastrophes.

2. While arterial backflow (reflux) maintains the brainstem viable, at least with the progressively symptomatic proximal or midbasilar presentations, the blood clot may be building up stepwise by new layers of clot, each blocking the small circumferential and perforating brainstem arteries (figure 6A). In fact, the reflux may furnish a continuous supply of coagulable blood to the site of thrombus formation. As the clot grows stepwise distally, ischemia at each sequential level of perforators triggers a crescendo of multiple new infarcts. This would be clearly at variance with the situation in anterior circulation large artery strokes, where a thromboembolus will initially become lodged and create a substantial penumbral tissue at risk, which the persistent ischemia will time-dependently necrotize into the eventual infarct core. In such infarctions, there is no successive clot formation and the extent of eventual infarction is



(A) In this drawing, the clot is building up sequentially onto the initial thromboembolus (clot 1) to the rostral direction. Analogous stepwise thrombus growth can naturally occur also to the caudal direction. The clinical syndrome is changing abruptly corresponding to stepwise advances in the deeply ischemic brainstem territory whenever a new set of perforating brainstem arteries is being occluded by new clot layers (2 and 3). (B) This drawing represents the situation where substantial reflux of arterial pressure gradient is being conveyed from the anterior territory through the posterior communicating arteries (arrows). In some instances, the initial thromboembolus may not lodge to the basilar tip but rather floats on this arterial reflux, thus avoiding attachment to the arterial wall. Instead, a piston-like or migrating clot movement can occur due to the systolic pressure waves separated by milliseconds pounding the clot from anterior and caudal directions. This can generate plasma flow between the clot and arterial wall (figures 2, F and G, and 4, D and E), which in turn maintains brittle patency of the brainstem perforator vasculature. Fibrinolytic therapy may detach a tethered clot and reinstate tissue circulation along with neurologic function, but this may be transient if the thrombus cannot be extracted or dissolved.

determined by the patency of collateral blood flow recruited at the outset in the infarct periphery. Indeed, it was shown recently that there is an interaction of time and collaterals in tissue loss. In the anterior circulation stroke, time alone is not a significant predictor of outcome but collaterals are. When collaterals are removed from the multivariable models, time becomes significant.¹⁵ The time window in which the tissue at risk can survive is determined by a physiologic tissue clock that starts to tick immediately.²⁴ This clock limits the tolerable period to a few hours, as we know from the pooled pivotal trials of thrombolysis.

3. In the proposed fundamentally different stepwise BAO clot growing either in anterior or caudal direction, in any patient with BAO who has survived the first hours without extensive brainstem infarction, the brainstem may be kept alive by multiple sources of residual and compensatory blood circulation. Besides backflow (reflux) from the anterior circulation through the PComs, considerable blood supply can be provided caudally from anastomotic vascular networks as well as the PICA-derived collaterals to both AICA and SCA systems. Anastomoses between the superficial brainstem arteries may become recruited by

abnormal hemodynamic and blood pressure gradient circumstances.

4. Finally, in some occasions a layer of plasma flow between the nonadherent and sometimes migrating blood clot and the vessel wall can maintain brittle patency of the BA side branches and brainstem perforators (figures 2, F and G, and 6B). Fibrinolytic mechanisms and therapeutic agents can prolong this plasma flow (figure 4, E and F), and make it possible to eventually terminate this hazardous situation by performing a thrombectomy. The recent work by Lescher et al.¹⁸ highlights the numerous intricate small BA side branches and perforators, and if enough attention is not paid to the existence of these vital vessels, even modern stentriever thrombectomy procedures will carry the risk of periprocedural brainstem necrosis despite perfect recanalization results.
5. As long as the brainstem structures have tolerable oligemia, a tissue clock will not start to tick. Consequently, the narrow time window for recanalization therapy is not in effect. On the contrary, recanalization at any point in time when the brainstem is still vital would rescue the situation by preventing imminent infarctions of vital brainstem structures associated with further accumulation of clot material.

However, once the brainstem perforating internal arteries have been occluded, there is no more time for rescue therapies. This concept is coherent with the observation that the presence of extensive posterior circulation infarctions as determined by pc-ASPECTS score is the single most significant prognostic baseline factor.⁶ To require lack of extensive brain infarction in the area supplied by the occluded artery before approving the patient for recanalization therapy is conceptually no different from what we require when we attempt to salvage the penumbra in the anterior circulation strokes.

THE WAY FORWARD The clinical management will probably shift towards rapid deployment of efficient endovascular techniques in reversing BAO. Our concepts emphasize that delay from symptom onset should not be regarded as an argument against aggressive therapies, if the parenchyma of the critically ischemic posterior circulation territory is still viable. On the other hand, MRI or noncontrast CT imaging of brainstem and additional parenchyma of the BA territory need to be systematically evaluated to reveal extended infarctions prior to costly treatments. Novel developments such as artefact-free CT image acquisition algorithms may assist evaluation of parenchymal structures in the posterior fossa.

The hypotheses proposed here can potentially be tested using novel techniques of determining microvascular perfusion and tissue viability in conjunction with ever perfecting recanalization techniques. It remains to be seen whether dynamic CT perfusion imaging or multimodal MRI can be refined to produce reliable estimates of tissue viability as in the anterior circulation. Centers that use primary angiography for patient selection will be able to use dynamic 3D rotational angiography and test in clinical trials tissue viability algorithms based on microvascular perfusion such as capillary index score.³¹ Clearly, evaluation of the patency of collaterals will be more important than today.

AUTHOR CONTRIBUTIONS

Drs. Lindsberg and Schroth conceptualized and designed the study. Drs. Schroth, Mattle, Pekkola, Strbian, and Sairanen collected data and participated in data analysis. Drs. Schroth and Pekkola analyzed all radiologic data. Dr. Lindsberg made the first draft and all others wrote parts of it and/or reviewed it critically.

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